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BIOGEN IDEC, INC and GENENTECH, INC.

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

'10CV0608BEN WVG

BIOGEN IDEC, INC., and GENENTECH, INC.

Plaintiffs,

v.

GLAXOSMITHKLINE LLC and GLAXO GROUP LIMITED,

Defendants.

CASE NO.

DECLARATORY RELIEF COMPLAINT FOR PATENT INFRINGEMENT

JURY TRIAL DEMANDED

Plaintiffs Biogen Idec, Inc. ("Biogen") and Genentech, Inc. ("Genentech") (collectively "Plaintiffs") for their Complaint against Glaxo Group Limited and GlaxoSmithKline LLC (collectively "Defendants" and "GSK") allege as follows:

NATURE OF THE CASE

1. This is an action for declaratory judgment of patent infringement of United States Patent No. 7,682,612. This action arises out of GSK's manufacture, use, sale, offer to sell and importation of GSK's ofatumumab, GSK's anti-CD20 antibody product marketed as Arzerra™ for treatment of chronic lymphocytic leukemia.

PARTIES

2. Plaintiff Biogen Idec Inc. is a Delaware Corporation with its principal place of business at 14 Cambridge Center, Cambridge, Massachusetts, 02142.

3. Plaintiff Genentech Inc. is a Delaware Corporation with its principal place of business at 1 DNA Way, South San Francisco, California, 94080.

4. On information and belief, Defendant GlaxoSmithKline LLC is a Delaware limited liability company having a principal place of business at One Franklin Plaza, Philadelphia, Pennsylvania, 19102.

5. On information and belief, Defendant Glaxo Group Limited d/b/a GlaxoSmithKline ("Glaxo Group Limited") is an English Corporation, having a principal place of business at Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB6 0NN, United Kingdom.

JURISDICTION AND VENUE

6. This is a civil action for declaratory judgment of patent infringement arising under the patent laws of the United States 35 U.S.C. § 1 et seq. and the Declaratory Judgment Act 28 U.S.C. §§ 2201 and 2202. This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

7. On information and belief, Glaxo Group Limited is in the business of manufacturing, marketing, importing and selling pharmaceutical drugs and biologic products, including antibody products such as Arzerra™. On information and belief, Glaxo Group Limited

directly or indirectly, through its affiliates and agents including GlaxoSmithKline LLC, manufactures, markets and sells pharmaceutical drugs and biologics products, including the Arzerra™ product, throughout the United States and in this judicial district. Thus, Glaxo Group Limited is subject to personal jurisdiction in this district because it regularly and continuously conducts business, including business directly related to Arzerra™, within the state of California.

8. On information and belief, GlaxoSmithKline LLC directly, or indirectly, manufactures, markets or sells pharmaceutical drug and biologic products, including antibody products such as Arzerra™, throughout the United States and in this judicial district. On information and belief, GlaxoSmithKline LLC purposefully has conducted and continues to conduct business in this judicial district. Thus, GlaxoSmithKline LLC is subject to personal jurisdiction in this district because it regularly and continuously conducts business, including business directly related to Arzerra™, within the state of California.

9. A real, immediate and substantial dispute exists between the parties given GSK's manufacture, sale, offering to sell, distributing and importing of Arzerra™ and the issuance of U.S. Patent No. 7,682,612 which covers methods of treating chronic lymphocytic leukemia by administering anti-CD20 antibodies such as Arzerra™.

10. Venue is proper in this district pursuant to 28 U.S.C. § 1391(b), (c) and (d).

FACTUAL BACKGROUND

11. On March 23, 2010 the United States Patent and Trademark Office duly and legally issued U.S. Patent No. 7,682,612 ("the '612 patent") to Biogen Idec Inc., the assignee of the named inventors Christine A. White and Antonio J. Grillo-Lopez and Genentech, Inc., the assignee of the named inventors Susan Desmond-Hellmann and John G. Curd. A copy of the '612 patent is attached as Exhibit A.

12. On information and belief, on or about October 26, 2009, GSK received approval from the United States Food & Drug Administration ("FDA") for the ofatumumab antibody product, an anti-CD20 antibody, also known as Arzerra™ for the treatment of chronic lymphocytic leukemia.

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13. On information and belief, after receiving FDA approval for Arzerra™, GSK began manufacturing, importing, offering to sell, selling and distributing Arzerra™ in the United States.

14. On information and belief, GSK's Arzerra™ product as sold includes a label which informs, encourages and promotes the use of this product for the treatment of chronic lymphocytic leukemia.

15. On information and belief, members of the medical community, who encompass but are not limited to, physicians, nurses, hospitals, medical clinics and medical facilities, pharmacists, pharmacies and pharmacist wholesalers, treat patients for chronic lymphocytic leukemia using Arzerra™ manufactured, sold and distributed by GSK.

16. Idec Pharmaceuticals was a San Diego, CA company. Idec Pharmaceuticals merged with Biogen in 2003.

17. Biogen has a research and corporate campus in San Diego, California, for cancer (oncology) research.

18. Inventors Christine A. White and Antonio J. Grillo-Lopez were employed by Idec Pharmaceuticals in San Diego, CA when the '612 patent was filed with the United States Patent and Trademark Office.

19. On information and belief, inventor Christine A. White is a resident of San Diego County, CA.

20. On information and belief, inventor Antonio J. Grillo-Lopez is a resident of San Diego County, CA.

21. Genentech has a manufacturing facility in Oceanside, San Diego County, California, for the manufacture of biologic products.

22. Genentech and Biogen co-market throughout the United States, including in this district, an anti-CD-20 antibody product known as Rituxan® for the treatment of chronic lymphocytic leukemia and other diseases.

23. Activities related to the creation and development of Rituxan® occurred primarily in San Diego, CA.

FIRST CLAIM FOR RELIEF
(Declaratory Judgment as to Inducing Infringement of the '612 Patent)

24. Plaintiffs repeat and reallege every allegation in paragraphs 1 through 23, as if fully set forth herein.

25. GSK received notice of the '612 patent at least as of its issue date on March 23, 2010 and/or the filing of the instant Complaint.

26. Through the conduct alleged above, GSK knowingly and actively induces and will induce members of the medical community, who encompass but are not limited to physicians, nurses, hospitals, medical clinics and medical facilities, pharmacists, pharmacies and pharmacist wholesalers for whom GSK manufactures and to whom GSK markets, offers to sell, sells and distributes Arzerra™, to directly infringe one or more claims of the '612 patent by their treatment of patients with Arzerra™ for chronic lymphocytic leukemia.

27. Plaintiffs are being and will be injured and damaged by GSK's knowing and active inducement of members of the medical community to directly infringe the '612 patent.

SECOND CLAIM FOR RELIEF
(Declaratory Judgment as to Contributory Infringement of the '612 Patent)

28. Plaintiffs repeat and reallege every allegation in paragraphs 1 through 23, as if fully set forth herein.

29. GSK received notice of the '612 patent at least as of its issue date on March 23, 2010 and/or the filing of the instant Complaint.

30. Through the sale, marketing and distribution of Arzerra™, GSK is contributing and will contribute to the infringement of one or more claims of the '612 patent by the medical community, who encompass but are not limited to physicians, nurses, hospitals, medical clinics and medical facilities, pharmacists, pharmacies and pharmacist wholesalers for whom GSK manufactures and to whom GSK markets, offers to sell, sells and distributes Arzerra™, through the medical community's treatment of patients with GSK's Arzerra™ for chronic lymphocytic leukemia. GSK manufactures, markets, offers to sell, sells and/or distributes Arzerra™ and will

continue to do so, knowing the same to be especially made or especially adapted for use in an infringement of the '612 patent. Upon information and belief, Arzerra™ is not a staple article or commodity of commerce suitable for substantial noninfringing use.

31. Plaintiffs are being and will be injured and damaged by GSK's contribution to the infringement of the '612 patent by members of the medical community.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray for relief as follows:

1. An order adjudging and decreeing that Defendant Glaxo Group Limited induces and will induce the direct infringement of the '612 patent;

2. An order adjudging and decreeing that Defendant GlaxoSmithKline LLC induces and will induce the direct infringement of the '612 patent;

3. An order adjudging and decreeing that Defendant Glaxo Group Limited contributes to and will contribute to the direct infringement of the '612 patent;

4. An order adjudging and decreeing that Defendant GlaxoSmithKline LLC contributes to and will contribute to the direct infringement of the '612 patent;

5. An order directing GSK to account for and pay to Plaintiffs all damages caused to Plaintiffs by reason of GSK's patent infringement, pursuant to 35 U.S.C. § 284, including increased damages under 35 U.S.C. § 284;

6. An award of pre-judgment and post-judgment interest on the damages caused to Plaintiffs by GSK;

7. A declaration that this case is exceptional and an award of attorneys' fees under 35 U.S.C. § 285 and costs and expenses in this action; and

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8. For all other relief the Court deems just and proper.

Dated: March 23, 2010

DLA PIPER LLP (US)

By _____
JOHN ALLCOCK
KATHRYN B. RILEY
ERICA J. PASCAL
Attorneys for Plaintiffs
BIOGEN IDEC, INC. and GENENTECH, INC.

DEMAND FOR JURY TRIAL

Plaintiffs Biogen Idec, Inc. and Genentech, Inc. hereby demand a jury trial.

Dated: March 23, 2010

DLA PIPER LLP (US)

By _____
JOHN ALLCOCK
KATHRYN B. RILEY
ERICA J. PASCAL
Attorneys for Plaintiffs
BIOGEN IDEC, INC. and GENENTECH, INC.

EXHIBIT A

(12) **United States Patent**
White et al.

(10) **Patent No.: US 7,682,612 B1**
(45) **Date of Patent: Mar. 23, 2010**

(54) **TREATMENT OF HEMATOLOGIC MALIGNANCIES ASSOCIATED WITH CIRCULATING TUMOR CELLS USING CHIMERIC ANTI-CD20 ANTIBODY**

(75) Inventors: **Christine A. White**, Rancho Santa Fe, CA (US); **Antonio J. Grillo-López**, Rancho Santa Fe, CA (US); **John G. Curd**, Hillsborough, CA (US); **Susan Desmond-Hellmann**, Alamo, CA (US)

(73) Assignees: **Biogen Idec Inc.**, Cambridge, MA (US); **Genentech, Inc.**, South San Francisco, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/436,347**

(22) Filed: **Nov. 9, 1999**

Related U.S. Application Data

(60) Provisional application No. 60/107,658, filed on Nov. 9, 1998.

(51) **Int. Cl.**
A61K 39/395 (2006.01)
A61K 51/00 (2006.01)

(52) **U.S. Cl.** **424/138.1**; 424/1.49; 424/133.1; 424/143.1; 424/144.1; 424/153.1; 424/156.1; 424/174.1; 530/350; 530/387.1; 530/387.3; 530/387.7; 530/388.1; 530/388.2; 530/388.73; 530/388.8; 530/388.85; 530/391.3

(58) **Field of Classification Search** 435/7.1, 435/7.2, 7.21, 7.23, 7.24, 7.25; 530/387.1, 530/387.3, 387.7, 388.1, 388.2, 388.73, 388.8, 530/388.85, 391.3, 350; 424/1.49, 133.1, 424/143.1, 144.1, 156.1, 174.1, 153.1, 138.1
See application file for complete search history.

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Primary Examiner—Alana M. Harris
(74) *Attorney, Agent, or Firm*—Sidley Austin LLP

(57) **ABSTRACT**

Chronic Lymphocytic Leukemia (CLL) may be treated with antibodies directed against the CD20 antigen.

60 Claims, No Drawings

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TREATMENT OF HEMATOLOGIC MALIGNANCIES ASSOCIATED WITH CIRCULATING TUMOR CELLS USING CHIMERIC ANTI-CD20 ANTIBODY

RELATED APPLICATIONS

This application claims benefit under 35 U.S.C. §119(e) to provisional application Ser. No. 60/107,658, filed Nov. 9, 1998, which is incorporated by reference in its entirety herein.

FIELD OF THE INVENTION

The present invention is directed to the treatment of hematologic malignancies associated with high numbers of circulating tumor cells by the administration of a therapeutically effective amount of a chimeric or humanized antibody that binds to the B-cell surface antigen Bp35 (CD20).

BACKGROUND OF THE INVENTION

The use of antibodies to CD20 as diagnostic and/or therapeutic agents for B-cell lymphoma has previously been reported. CD20 is a useful marker or target for B-cell lymphomas as this antigen is expressed at very high densities on the surface of malignant B-cells, i.e., those B-cells wherein unabated proliferation can lead to B-cell lymphomas.

CD20 or Bp35 is a B-lymphocyte-restricted differentiation antigen that is expressed during early pre-B-cell development and remains until plasma cell differentiation. It is believed that the CD20 molecule may regulate a step in the B-cell activation process which is required for cell cycle initiation and differentiation. Moreover, as noted, CD20 is expressed at very high levels on neoplastic ("tumor") B-cells.

Previous reported therapies involving anti-CD20 antibodies have involved the administration of a therapeutic anti-CD20 antibody either alone or in conjunction with a second radiolabeled anti-CD20 antibody, or a chemotherapeutic agent.

In fact, the Food and Drug Administration has approved the therapeutic use of one such therapeutic anti-CD20 antibody, RITUXAN® (rituximab), for use in treatment of relapsed and previously treated low-grade non-Hodgkin's lymphoma (NHL). Also, the use of RITUXAN® (rituximab) in combination with a radiolabeled murine anti-CD20 antibody has been suggested for the treatment of B-cell lymphoma.

However, while anti-CD20 antibodies and, in particular, RITUXAN® (rituximab) have been reported to be effective for treatment of B-cell lymphomas, such as non-Hodgkin's lymphoma, it would be beneficial if effective antibody treatments for other malignancies could be developed. More specifically, it would be beneficial if anti-CD20 antibodies could be used for treating other types of malignancies.

BRIEF DESCRIPTION OF THE INVENTION

Toward that end, the present inventors have developed a novel treatment for hematologic malignancies characterized by a high number of tumor cells in the blood involving the administration of a therapeutically effective amount of an anti-CD20 antibody. In the preferred embodiments, such anti-CD20 antibody will comprise a chimeric, humanized, or human anti-human CD20 antibody. Examples of such hematologic malignancies include B-pro-lymphocytic leukemia (B-PLL), chronic lymphocyte leukemia (CLL), and transformed non-Hodgkin's lymphoma.

Thus, it is an object of the invention to provide a novel treatment for hematologic malignancies comprising the administration of an anti-CD20 antibody.

It is a more specific object of the invention to provide a novel treatment for B-prolymphocytic leukemia (B-PLL), chronic lymphocytic leukemia (CLL) or transformed non-Hodgkin's lymphoma comprising the administration of an anti-CD20 antibody.

It is an even more specific object of the invention to treat B-prolymphocytic leukemia (B-PLL) or chronic lymphocytic leukemia (CLL) comprising administration of a therapeutically effective amount of RITUXAN® (rituximab).

DETAILED DESCRIPTION OF THE INVENTION

The invention involves the discovery that hematologic malignancies and, in particular, those characterized by high numbers of tumor cells in the blood may be effectively treated by the administration of a therapeutic anti-CD20 antibody. These malignancies include, in particular, CLL, B-PLL and transformed non-Hodgkin's lymphoma.

This discovery is surprising notwithstanding the reported great success of RITUXAN® (rituximab) for the treatment of relapsed and previously treated low-grade non-Hodgkin's lymphoma. In particular, this discovery is surprising given the very high numbers of tumor cells observed in such patients and also given the fact that such malignant cells, e.g., CLL cells, typically do not express the CD20 antigen at the high densities which are characteristic of some B-cell lymphomas, such as relapsed and previously-treated low-grade non-Hodgkin's lymphomas. Consequently, it could not have been reasonably predicted that the CD20 antigen would constitute an appropriate target for therapeutic antibody therapy of such malignancies.

Treatment of hematologic malignancy, such as CLL, B-PLL and transformed non-Hodgkin's lymphoma, according to the invention will comprise the administration of a therapeutically effective amount of an anti-CD20 antibody, which administration may be effected alone or in conjunction with other treatment(s), e.g., chemotherapy, radiotherapy (e.g., whole body irradiation, or treatment with radiolabeled antibodies). In addition, combination therapy with cytokines may be useful to upregulate CD20 on the surface of the lymphoma cells.

In the preferred embodiment, the anti-CD20 antibody will bind CD20 with high affinity, i.e., ranging from 10^{-5} to 10^{-9} M. Preferably, the anti-CD20 antibody will comprise a chimeric, primate, PRIMATIZED®, human, or humanized antibody. Also, the invention embraces the use of antibody fragments, e.g., Fab's, Fv's, Fab's, $F(ab)_2$, and aggregates thereof.

A chimeric antibody is intended to refer to an antibody with non-human variable regions and human constant regions, most typically rodent variable regions and human constant regions.

A PRIMATIZED® antibody refers to an antibody with primate variable regions, e.g., complementarity-determining regions (CDRs), and human constant regions. Preferably, such primate variable regions are derived from an Old World monkey.

A humanized antibody refers to an antibody with substantially human framework and constant regions, and non-human CDRs. "Substantially" refers to the fact that humanized antibodies typically retain at least several donor framework residues (of non-human parent antibody from which CDRs are derived).

Methods for producing chimeric, primate, PRIMATIZED®, humanized, and human antibodies are well known in the art. See, e.g., U.S. Pat. No. 5,530,101, issued to Queen et al, U.S. Pat. No. 5,225,539, issued to Winter et al, U.S. Pat. Nos. 4,816,397 and 4,816,567, issued to Boss et al, and Cabilly et al, respectively, all of which are incorporated by reference in their entirety.

The selection of human constant regions may be significant to the therapeutic efficacy of the subject anti-CD20 antibody. In the preferred embodiment, the subject anti-CD20 antibody will comprise human, gamma 1, or gamma 3 constant regions and, more preferably, human gamma 1 constant regions. The use of gamma 1 anti-CD20 antibodies as therapeutics is disclosed in U.S. Pat. No. 5,500,362, issued to Robinson et al.

Methods for making human antibodies are also known and include, by way of example, production in SCID mice, and in vitro immunization.

As noted, a particularly preferred chimeric anti-CD20 antibody is RITUXAN® (rituximab), which is a chimeric gamma 1 anti-human CD20 antibody. The complete nucleic acid sequence encoding this antibody and the corresponding amino acid sequences of the heavy chain and light chain variable domains may be found in U.S. Pat. No. 5,736,137, which is incorporated by reference in its entirety. This antibody, which is produced in a proprietary CHO cell expression system commercialized by IDEC Pharmaceuticals Corporation, may be made by a CHO cell transfectoma comprising the vector DNA present in the *E. coli* host cell deposited on Nov. 4, 1992, under the provisions of the Budapest Treaty at the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Va. 20110-2209, under accession no. 69119. This deposit was determined to be viable and will be replaced should it become non-viable during the term of deposit. This deposit was made irrevocably available upon issuance of U.S. Pat. No. 5,736,137 and is available without restriction from the ATCC. This deposit will also be available without restriction during the lifetime of any patent that may issue based on this application.

The subject anti-CD20 antibody will be administered by various routes of administration, typically parenteral. This is intended to include intravenous, intramuscular, subcutaneous, rectal, and vaginal administration, with intravenous infusion being preferred.

The anti-CD20 antibody will be formulated for therapeutic usage by standard methods, e.g., by addition of pharmaceutically acceptable buffers, e.g., sterile saline, sterile buffered water, propylene glycol, and combinations thereof.

Effective dosages will depend on the specific antibody, condition of the patient, age, weight, or any other treatments, among other factors. Typically effective dosages will range from about 0.001 to about 30 mg/kg body weight, more preferably from about 0.01 to 25 mg/kg body weight, and most preferably from about 0.1 to about 20 mg/kg body weight.

Such administration may be effected by various protocols, e.g., weekly, bi-weekly, or monthly, dependent on the dosage administered and patient response. Also, it may be desirable to combine such administration with other treatments, e.g., radioactive therapy, both targeted and non-targeted, chemotherapies, and lymphokine or cytokine administration, e.g., interleukins, interferons, TNFs, colony stimulating factors, etc.

Typically, treatment will be effected weekly, for about 2 to 10 weeks, more typically about 4 weeks. A particularly preferred dosage regimen will comprise administration of about 375 mg/m^2 weekly for a total of four infusions. Also, stepped-up dosing schedules may be even more preferable.

If radiation is used in conjunction with the therapeutic anti-CD20 antibody, it is preferred that an yttrium-labeled anti-CD20 antibody be utilized, such as the one disclosed in U.S. Pat. No. 5,736,137, incorporated by reference in its entirety herein. This antibody, [^{90}Y]-2B8-MX-DTPA, has reported efficacy in the treatment of B-cell lymphoma. The hybridoma that produces the 2B8 antibody was deposited at the American Type Culture Collection under accession no. HB 11388 on Jun. 22, 1993, under the provisions of the Budapest Treaty, and was made irrevocably available upon issuance of U.S. Pat. No. 5,736,137, without any restrictions. This hybridoma was found to be viable and will be replaced during the lifetime of any patent that issues based on this application, should it become non-viable.

A particularly preferred chemotherapeutic regimen that may be used in conjunction with the subject antibody immunotherapy comprises CHOP chemotherapy, which comprises the administration of a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone. Other known chemotherapeutics include methotrexate, cisplatin, toremifene, and tamoxifen.

The following examples are not intended, nor are they to be construed, as limiting the invention. The examples are intended to provide clinical evidence in support of the efficacy of the invention.

EXAMPLE 1

Two patients in whom we noted rapid reduction of blood tumor cells, which was associated with severe pulmonary infusion-related toxicity and thrombocytopenia, were studied. Also, two additional patients were collected from physician-submitted reports of adverse events related to RITUXAN® (rituximab) treatment. Pretreatment characterization of these patients included a median age of 60 years (range 26-73) with the diagnosis of B-prolymphocytic leukemia (B-PLL), chronic lymphocytic leukemia (CLL), or transformed non-Hodgkin's lymphoma. All of these patients had elevated leukocyte counts as a consequence of blood tumor involvement, bulky adenopathy and organomegaly. All four patients developed a unique syndrome of severe infusion-related reactions characterized by fever, rigors, bronchospasm with associated hypoxemia, requiring temporary cessation of RITUXAN® (rituximab) therapy. Concurrent with these symptoms, a rapid decrement in circulating tumor cell load (mean pretreatment 98×10^3L; range 73-132 vs. mean post-treatment 11×10^3L; range 37-24.6) with mild electrolyte evidence of rapid tumor lysis was observed. Thrombocytopenia, a finding not commonly associated with RITUXAN® (rituximab) therapy, was noted in all four patients (mean pretreatment 145×10^3L; range 57-277 vs. mean post-treatment $Sn\times10^9$/L; range 2-120), requiring transfusion in one case. Symptoms of this syndrome required hospitalization but resolved with supportive care. Subsequent RITUXAN® (rituximab) treatment were well tolerated in all patients.

Two subsequent patients with CLL have been treated with high blood tumor counts utilizing stepped-up dosing (100 mg day 1 followed by the rest of therapy on day 1) with demonstrated efficacy, thrombocytopenia but minimal infusion-related toxicity. RITUXAN® (rituximab) administration in patients with hematologic malignancies who have blood tumor cell involvement may be associated with a higher frequency of severe initial infusion-related reactions and thrombocytopenia mandating careful clinical monitoring. Given the preliminary activity of RITUXAN® (rituximab) in these patients, future studies in CLL and PLL, utilizing a stepped-up dosing schedule, are to be conducted.

EXAMPLE 2

Unlabeled immunoglobulins (monoclonal antibodies, Mabs) are attractive for the treatment of NHL as they may: mediate cytotoxicity with complement (CDC) or effector cells (ADCC); effect apoptosis; be less toxic, less immunogenic and possibly more effective than toxin- or drug-conjugated Mabs; not require the complex procedures needed for radiolabeled Mab therapy (radioimmunotherapy, RIT), and not produce the myelosuppression typical of high-dose RIT.

Until recently, use of Mabs in the treatment of hematologic malignancies has been limited. However, the chimeric anti-CD20 Mab, RITUXAN® (rituximab), has a low toxicity profile and significant clinical efficacy and is now approved by the U.S. Food and Drug Administration (November 1997) and in the E.U. (June 1998) for the treatment of relapsed or refractory, low-grade or follicular (R-LG/F) NHL. In a single-agent phase III clinical trial, of 166 patients with R-LG/F NHL treated with RITUXAN® (rituximab) at 375 mg/m^2 weekly for four infusions (study 102-05), the overall response rate (ORR) was 48% (6% complete response (CR) and 42% partial response (PR)). Median time to progression for responders was 13.1 months and duration of response was 11.2 months. Median circulating B-lymphocyte counts dropped to zero following the first dose. CD3, CD4, CD8 and NK cell counts remained unchanged. B-cell recovery in peripheral blood began at 6-9 months and was complete by 9-12 months. No significant changes in serum complement levels were noted. The mechanism for action remains unresolved with CDC, ADCC, apoptosis and/or others being considered. In spite of the absence of a clinical/laboratory correlation, the contribution of CDC cannot be discounted. We have seen a correlation between higher absolute NK cell count at baseline and response to the Mab.

Cell Type	# Patients CR + PR	Abs. Count	# Patients NR	Abs. Count	P-value
NK	98	180	15	98	0.02
MK + ANC	98	185	15	102	0.02
ANC	101	3.7	15	3.4	0.40
CD3+	98	761	15	576	0.37
Platelets	101	187	15	206	0.32

Note: N = 166 patients from study 102-05, and 37 from 102-06. Abs. Count: NK, CD3 = cells/mm^3; ANC, Pts. = cells x 10^3/mm^3. P value for the difference between Abs. Counts.

ADCC may be an important mechanism for the clinical activity seen in patients treated with RITUXAN® (rituximab). Agents which enhance effector cell number and activity may synergize with the Mab. Studies of RITUXAN® (rituximab) in combination with cytokines, e.g., Il-2, G-CSF, GM-CSF, INF, are also ongoing.

EXAMPLE 3

Phase I/II Study of RITUXAN® (rituximab) in CLL

RITUXAN® (rituximab) is a monoclonal antibody targeting CD20 that has significant activity in the treatment of low-grade lymphoma (LGL). When given at a dosage of 375 mg/m^2 weekly for four weeks the response rate in relapsed patients was 43% (McClaughlin et al., KOO, Vol. 14, 1998). Patients with small lymphocytic lymphoma (SLL) had lower response rates (13%) than patients with other subtypes of LGL and lower serum levels of RITUXAN® (rituximab). Reduced response seen in SLL could be related to lower density of CD20 antigen and/or higher circulating B-cell counts. Both factors would be expected to impact (negatively) on response seen in CLL.

In an attempt to maximize activities in CLL we are conducting a Phase I/II study. All patients receive a first dose of 375 mg/m^2 to minimize infusion related side effects. Subsequent weekly dosages (3) remain the same but are given at an increased dose level. Sixteen patients have been treated at dosages of 500-1500 mg/m^2. Median age was 66 years (range, 25-78). Eighty-one percent had end-stage III-IV disease. Median white blood cell count was 40x10^9/L (range, 4-200), Hgb 11.6 g/dl (range, 7.7-14.7), platelets 75x10^9/L (range, 16-160), median β_2 microglobulin was 4.5 mg/L (range, 3.1-9.2). Median numbers of prior therapies was 2.5 (range 1-9). Sixty percent of patients were refractory to treatment. Two patients developed severe hypertension with the first dose (375 mg/m^2); another one received further therapy. Toxicity at subsequent escalated dosages has been mild although no patient at the 1500 mg/m^2 dose level has been fully evaluated. Eight patients have completed therapy (4 at 500 mg/m^2, 3 at 650 mg/m^2, 1 at 825 mg/m^2). One patient treated at 560 mg/m^2 achieved full remission. One patient has progressive lymphocytosis on treatment and all other patients had reduction in peripheral blood lymphocytosis but less effect on lymph nodes. Dose escalation studies are ongoing.

EXAMPLE 4

Use of Cytokines to Upregulate the Expression of CD20

Another approach to improving response in CLL patients is to upregulate the CD20 antigen using cytokines. In an in vitro study, mononuclear cells from CLL patients were incubated for 24 hours with various cytokines. Flow cytometry results showed significant up-regulation by IL-4, GM-CSF, and TNF-alpha. (Venugopal P, Sivaraman S, Huang X, Chopra H, O'Brein T, Jajeh A, Preisler H. Upregulation of CD20 expression in chronic lymphocytic leukemia (CLL) cells by in vitro exposure to cytokines. *Blood* 1998; 10:247a.) In fact, recent data suggest that the upregulation of CD20 observed on CLL cells may be limited to tumor cells (Venogopal et al. Poster—PanPacific Lymphoma meeting, June 1999. Cytokine-induced upregulation of CD20 antigen expression in chronic lymphocytic leukemia (CLL) cells may be limited to tumor cells). Preliminary data also suggest that interferon alpha also upregulates CD20 on CLL cells after only 24 hours when applied at a concentration of 500 to 1000 U/ml.

Thus, by administering certain cytokines to CLL patients prior to or concurrently with administration of RITUXAN® (rituximab), the expression of CD20 on the surface of malignant B-cells may be upregulated, thereby rendering CD20, as well as other cell surface markers such as CD19, a more attractive target for immunotherapy.

A collaborative study has been initiated to test for optimal cytokine doses for CD20 upregulation in vivo. The study protocol involves treating ten patients initially with GM-CSF at 250 mcg/m^2 SQ QD X 3, ten patients with IL-4 mcg/kg SQ QD X 3, and ten patients with G-CSF at 5 mcg/kg SQ QD X 3. Mononuclear cells will be separated by FICOLL® (sucrose-epichlorohydrin copolymer) Hypaque centrifugation

for apoptotic studies to determine if upregulation of CD20 translates to enhanced killing of tumor cells by RITUXAN® (rituximab).

EXAMPLE 5

Combination Antibody and Chemotherapy Protocol

Antibody treatment of CLL can be combined with other conventional chemotherapeutic treatments known to be useful for the treatment of CLL. The most frequently used single agent for CLL is chlorambucil (LEUKERAN®), given either as 0.1 mg/kg daily or 0.4 to 1.0 mg/kg every 4 weeks. Chlorambucil is often combined with oral prednisone (30 to 100 mg/m^2/d), which is useful in the management of autoimmune cytopenias. Cyclophosphamide is an alternative to chlorambucil, the usual dose being 1-2 g/m^2 every 3-4 weeks together with vincristine and steroids (e.g., COP regimen).

Various drug combinations have been used for CLL, including COP (cyclophosphamide, Oncovin, and prednisone), and CHOP (these three drugs plus doxorubicin). Fludarabine has shown an effect in the treatment of CLL, and gave an ORR of 50% in a group of patients treated with 25-30 mg/m^2/d every 3-4 weeks. See www.cancernetwork.com. Some patients have been shown to be refractory for fludarabine. Such patients may also be resistant to 2-CdA because often, patients who are refractory to fludarabine are also refractory to 2-CDA (O'Brien et al. N. Engl. J. Med. 330: 319-322 (1994)).

Hence, anti-CD20 antibody therapy will be particularly useful for patients who are refractory or who have relapsed after treatment with chemotherapeutic drugs. RITUXAN® (rituximab) therapy may also be combined with radiotherapy in these patients. TBI with a low fraction size of 15 cGy to total doses of 75 to 150 cGy has been shown to be effective in about one-third of patients.

A Phase II trial is currently being conducted by CALGB in CLL patients. RITUXAN® (rituximab) and fludarabine are administered concurrently, followed by RITUXAN® (rituximab) consolidation versus fludarabine induction followed by RITUXAN® (rituximab). The goals of the study are (1) to determine in fludarabine treated CLL patients the complete response (CR) rate and toxicity profile of concurrent and consolidative RITUXAN® (rituximab) therapy (Arm I) and of consolidative RITUXAN® (rituximab) therapy (Arm II); (2) to assess the CR rate in patients receiving concurrent therapy with RITUXAN® (rituximab) and fludarabine (the inductive phase of Arm I); (3) to assess the frequency of conversion of a partial response (PR) to a CR or stable disease to either PR or CR in CLL patients receiving consolidative therapy with RITUXAN® (rituximab); (4) to follow the effects of therapy with RITUXAN® (rituximab) and fludarabine on the immunologic markers CD4, CD8, IgG, IgA and IgM; and (5) to examine progression-free survival and overall survival in Arms I and II.

Although the present invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding it will be apparent that certain changes and modifications may be practical within the scope of the appended claims.

What is claimed is:

1. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia, wherein the method does not include treatment with a radiolabeled anti-CD20 antibody.

2. A method according to claim 1, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 0.001 to about 30 mg/kg.

3. A method according to claim 1, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 0.01 to about 25 mg/kg.

4. A method according to claim 1, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 0.1 to about 20 mg/kg.

5. A method according to claim 1, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 375 mg/m^2.

6. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 500 to about 1500 mg/m^2, wherein the method does not include treatment with a radiolabeled anti-CD20 antibody.

7. A method according to claim 6, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 500 mg/m^2.

8. A method according to claim 1 or 6, wherein the patient has relapsed following previous treatment for the chronic lymphocytic leukemia.

9. A method according to claim 1 or 6, wherein the patient is refractory to a treatment previously administered for the chronic lymphocytic leukemia.

10. A method according to claim 9, wherein the patient is refractory to fludarabine.

11. A method according to claim 1 or 6, wherein the anti-CD20 antibody is a chimeric antibody.

12. A method according to claim 11, wherein the anti-CD20 antibody is rituximab.

13. A method according to claim 1 or 6, wherein the anti-CD20 antibody is a humanized antibody.

14. A method according to claim 1 or 6, wherein the anti-CD20 antibody is a human antibody.

15. A method according to claim 1 or 6, wherein the anti-CD20 antibody comprises a CD20-binding fragment of a chimeric, humanized, or human antibody.

16. A method according to claim 1 or 6, wherein the anti-CD20 antibody is administered to the patient repeatedly.

17. A method according to claim 16, wherein the anti-CD20 antibody is administered to the patient weekly.

18. A method according to claim 16, wherein the anti-CD20 antibody is administered to the patient weekly for about 2 to 10 weeks.

19. A method according to claim 16, wherein the anti-CD20 antibody is administered to the patient biweekly.

20. A method according to claim 16, wherein the anti-CD20 antibody is administered to the patient monthly.

21. A method according to claim 1 or 6, wherein the anti-CD20 antibody is administered to the patient parenterally.

22. A method according to claim 21, wherein the anti-CD20 antibody is administered to the patient by intravenous infusion.

23. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia, wherein the anti-CD20 antibody therapy is combined with chemotherapy, wherein the method does not include treatment with a radiolabeled anti-CD20 antibody.

24. A method according to claim 23, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 0.001 to about 30 mg/kg.

25. A method according to claim 23, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 0.01 to about 25 mg/kg.

26. A method according to claim 23, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 0.1 to about 20 mg/kg.

27. A method according to claim 23, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 375 mg/m^2.

28. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 500 to about 1500 mg/m^2, wherein the anti-CD20 antibody therapy is combined with chemotherapy, and wherein the method does not include treatment with a radiolabeled anti-CD20 antibody.

29. A method according to claim 28, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 500 mg/m^2.

30. A method according to claim 23 or 28, wherein the patient has relapsed following previous treatment for the chronic lymphocytic leukemia.

31. A method according to claim 23 or 28, wherein the patient is refractory to a treatment previously administered for the chronic lymphocytic leukemia.

32. A method according to claim 31, wherein the patient is refractory to fludarabine.

33. A method according to claim 23 or 28, wherein the anti-CD20 antibody is a chimeric antibody.

34. A method according to claim 33, wherein the anti-CD20 antibody is rituximab.

35. A method according to claim 23 or 28, wherein the anti-CD20 antibody is a humanized antibody.

36. A method according to claim 23 or 28, wherein the anti-CD20 antibody is a human antibody.

37. A method according to claim 23 or 28, wherein the anti-CD20 antibody comprises a CD20-binding fragment of a chimeric, humanized, or human antibody.

38. A method according to claim 23 or 28, wherein the anti-CD20 antibody is administered to the patient repeatedly.

39. A method according to claim 38, wherein the anti-CD20 antibody is administered to the patient weekly.

40. A method according to claim 38, wherein the anti-CD20 antibody is administered to the patient weekly for about 2 to 10 weeks.

41. A method according to claim 38, wherein the anti-CD20 antibody is administered to the patient biweekly.

42. A method according to claim 38, wherein the anti-CD20 antibody is administered to the patient monthly.

43. A method according to claim 23 or 28, wherein the anti-CD20 antibody is administered to the patient parenterally.

44. A method according to claim 43, wherein the anti-CD20 antibody is administered to the patient by intravenous infusion.

45. A method according to claim 23 or 28, wherein the anti-CD20 antibody therapy and the chemotherapy are administered to the patient concurrently.

46. A method according to claim 23 or 28, wherein the chemotherapy comprises chlorambucil.

47. A method according to claim 23 or 28, wherein the chemotherapy comprises cyclophosphamide.

48. A method according to claim 47, wherein the chemotherapy comprises cyclophosphamide, vincristine, and prednisone (COP).

49. A method according to claim 47, wherein the chemotherapy comprises cyclophosphamide, vincristine, prednisone, and doxorubicin (CHOP).

50. A method according to claim 23 or 28, wherein the chemotherapy comprises vincristine.

51. A method according to claim 23 or 28, wherein the chemotherapy comprises prednisone.

52. A method according to claim 23 or 28, wherein the chemotherapy comprises doxorubicin.

53. A method according to claim 23 or 28, wherein the chemotherapy comprises fludarabine.

54. A method according to claim 23 or 28, wherein the chemotherapy comprises methotrexate.

55. A method according to claim 23 or 28, wherein the chemotherapy comprises cisplatin.

56. A method according to claim 23 or 28, wherein the chemotherapy comprises toremifene.

57. A method according to claim 23 or 28, wherein the chemotherapy comprises tamoxifen.

58. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia, wherein the patient is refractory to fludarabine previously administered for the chronic lymphocytic leukemia, and wherein the method does not include treatment with a radiolabeled anti-CD20 antibody.

59. A method according to claim 6, 28, or 58, wherein radiation is not used in conjunction with the anti-CD20 antibody.

60. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering a therapeutic non-radiolabeled anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia, wherein radiation is not used in conjunction with said anti-CD20 antibody.

* * * * *

JS 44 (Rev. 12/07)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS
BIOGEN IDEC, INC. and GENENTECH, INC.

DEFENDANTS
GLAXOSMITHKLINE LLC and GLAXO GROUP LIMITED

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10 MAR 23 PM 4:20
CLERK, U.S. DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA
BY: MTB DEPUTY

(b) County of Residence of First Listed Plaintiff San Diego
(EXCEPT IN U.S. PLAINTIFF CASES)

County of Residence of First Listed Defendant Philadelphia, PA
(IN U.S. PLAINTIFF CASES ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE LAND INVOLVED.

(c) Attorney's (Firm Name, Address, and Telephone Number)
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'10CV0608 BEN WVG

II. BASIS OF JURISDICTION (Place an "X" in One Box Only)

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (Place an "X" in One Box for Plaintiff and One Box for Defendant)
(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT (Place an "X" in One Box Only)

CONTRACT
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- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excl. Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability
- ☐ 196 Franchise

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

PERSONAL INJURY
- ☐ 362 Personal Injury—Med. Malpractice
- ☐ 365 Personal Injury — Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 445 Amer. w/Disabilities - Employment
- ☐ 446 Amer. w/Disabilities – Other
- ☐ 440 Other Civil Rights

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence

Habeas Corpus:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

FORFEITURE/PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 Liquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regs.
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 730 Labor/Mgmt.Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl. Ret. Inc. Security Act

IMMIGRATION
- ☐ 462 Naturalization Application
- ☐ 463 Habeas Corpus – Alien Detainee
- ☐ 465 Other Immigration Actions

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☒ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 480 Consumer Credit
- ☐ 490 Cable/Sat TV
- ☐ 810 Selective Service
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Information Act
- ☐ 900Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes

V. ORIGIN (Place an "X" in One Box Only)
☒ 1 Original Proceeding | ☐ 2 Removed from State Court | ☐ 3 Remanded from Appellate Court | ☐ 4 Reinstated or Reopened | ☐ 5 Transferred from another district (specify) | ☐ 6 Multidistrict Litigation | ☐ 7 Appeal to District Judge from Magistrate Judgment

VI. CAUSE OF ACTION
Cite the U.S. Civil Statute under which you are filing **(Do not cite jurisdictional statutes unless diversity):**
35 U.S.C. Section 1 et seq.
Brief description of cause:
Patent infringement

VII. REQUESTED IN COMPLAINT: ☐ CHECK IF THIS IS A **CLASS ACTION** UNDER F.R.C.P. 23 **DEMAND $**
CHECK YES only if demanded in complaint: **JURY DEMAND:** ☒ Yes ☐ No

VIII. RELATED CASE(S) IF ANY (See instructions): JUDGE _____ DOCKET NUMBER _____

DATE
March 23, 2010

SIGNATURE OF ATTORNEY OF RECORD

FOR OFFICE USE ONLY
RECEIPT # 11442 AMOUNT $350 APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____
MTB 03-23-10

Court Name: USDC California Southern
Division: 3
Receipt Number: CAS011442
Cashier ID: mbain
Transaction Date: 03/23/2010
Payer Name: DLA PIPER

CIVIL FILING FEE
For: BIOGEN AND GENENTECH V GLAXOSM
Case/Party: D-CAS-3-10-CV-000608-001
Amount: $350.00

CHECK
Check/Money Order Num: 592242
Amt Tendered: $350.00

Total Due: $350.00
Total Tendered: $350.00
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charged for any returned check.